Leptin in a Lean Population of Filipino Adolescents

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ABSTRACT   To clarify the role of leptin as a signal of energy status in humans, this study investigated the relationship of leptin to measures of body composition, maturity, and lifestyle factors in a lean sample of 293 male and 303 female Filipino adolescents (age 14–16 years). Participants were selected from the Cebu Longitudinal Health and Nutrition Survey, a representative birth cohort study begun in 1983. Using IOTF criteria, the prevalence of overweight (2.2%) and obesity (0.3%) were extremely low, and leptin levels were among the lowest reported in any healthy population (mean: 0.78 and 3.57 ng/dl in males and females). As expected, adiposity was the strongest predictor of leptin, with triceps skinfold explaining 40.2 and 30.6% of leptin variance in males and females. In females, subscapular skinfold was a significant predictor of leptin independent of triceps, while no anthropometric measure predicted leptin independent of triceps in males. There were few relationships between lifestyle factors and leptin independent of adiposity. In males, leptin levels varied little across most of the triceps distribution, suggesting that the leptin-adipose regulatory system is sensitive to very small changes in leptin in lean populations, at least among males. These findings add to the small but growing list of studies documenting differences in leptin biology among chronically lean populations. Am J Phys Anthropol 132:642–649, 2007.   © 2007 Wiley-Liss, Inc.

Leptin is a hormone secreted by adipocytes in proportion to the quantity of fat stored in the cell (Fruhbeck et al., 1998; Jequier, 2002). As a correlate of body fat, leptin allows leptin-sensing regions of the brain to monitor changes in energy status, and to adjust intake and expenditure to maintain a stable body weight (Weigle et al., 1995; Schwartz et al., 2000). Given its wide-ranging effects on energy metabolism, the hormone has been a focus of research on the endocrine regulation of appetite and weight gain (Trayhurn, 2001). In addition, its broad effects on functions like reproduction (Kiess et al., 1998; Messinis and Milingos, 1999), growth (Steppan et al., 2000; Kishida et al., 2005), immunity (Lord et al., 1998; Fantuzzi and Faggioni, 2000), and the brain (Ahima et al., 2000), demonstrate the hormone's importance in helping the body manage patterns of energy expenditure in response to changes in energy status.

While the hormone's role as a signal of energy stores is its defining feature (Bowles and Kopelman, 2001), it is now clear that the amount of leptin secreted by an adipocyte is influenced by factors other than its fat content. For instance, leptin secretion may be modulated by dietary intake and by hormones like insulin, glucocorticoids, and the sex steroids (Blum et al., 1997; Heptulla et al., 2001; Chan et al., 2002). Males have lower leptin levels than females for a given fat mass (Saad et al., 1997), and this partly reflects direct effects of sex steroids on leptin production in the adipocyte (Shimizu et al., 1997; Dicker et al., 2004). Leptin production also differs by regional depot, with the more metabolically-labile central adipose tissue producing less leptin than fat cells in subcutaneous, and especially, peripheral depots (Frederich et al., 1995; Minocci et al., 2000). By influencing leptin concentration independent of the fat present in the cell, these factors would seem to decouple the signal of circulating leptin from the quantity of mobilizable energy stores available to the organism.

The vast majority of leptin research has focused on clinical samples with relatively high levels of adiposity and high body mass indices (BMI), and these studies consistently report strong correlations between adiposity and circulating leptin (Jequier, 2002). In contrast, circulating leptin is only weakly correlated, or not correlated at all, with adiposity in some lean human populations, or among wild primates with chronically low energy sufficiency or body mass (Banks et al., 2001; Bribiescas, 2001, 2005; Moore et al., 2002; Lindegärde et al., 2004). Under the assumption that an abundance of body fat is an evolutionarily-novel condition, these differences in the relationship between adiposity and leptin in lean populations raise additional questions about the hormone's role as a signal of energy status (Banks et al., 2001; Collinson et al., 2005).

To clarify the relationship between adiposity and leptin among the lean, the present study documents leptin concentrations and anthropometric, maturational and lifestyle correlates in a representative sample of 596 Filipino adolescents in whom overweight and obesity are nearly absent. Even as these adolescents are lean by the standards of many US, European, or Asian populations, the rate of overweight and obesity among the subjects' mothers, and in the general adult population in the Philippines, have increased markedly in the past two decades (Adair, 2004). Thus, the second goal of this study

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is to document the metabolic state of this adolescent population prior to the age-related increase in weight gain that is emerging as an important influence on adult health in the Philippines.

MATERIALS AND METHODS

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based birth cohort study of mothers and their infants born in 1983–1984 (Popkin et al., 1990; Adair et al., 2001; Kuzawa et al., 2003). Body weight, height, waist circumference, triceps, and subscapular skinfold thicknesses were measured using standard anthropometric techniques (Lohman et al., 1988). The body mass index (BMI) was calculated as the ratio of weight (kg)/height (m^2). During the 1998–1999 follow-up, the child's dietary intake was measured using two 24-h recalls on consecutive days and the mean was used in analyses. Energy and fat intake were calculated using Philippines Food Composition Tables produced by the Food and Nutrition Research Institute of the Philippines (FNRI, 1990). Physical activity was assessed using the Caltrac, a small device that attaches to the waist and records a cumulative tally of motion, which in turn is used along with body weight to estimate expended calories (Westerterp, 1999). Among males, maturational status was assessed by self-rated 5-level pubic hair (PH) stages which represent maturational stages identified by Tanner (1962). The self assessment was validated against physician assessment and found to have an acceptable level of agreement (55% exact correspondence, 42% within one stage). Females were asked to recall the month and year of first menstruation during prospective follow-up surveys and the sample was then stratified on quartiles of maturational status (Koo and Rohan, 1997). When data were collected for the 1998–2000 survey, girls were completely surveyed before boys. Consequently, boys were roughly 1 year older than girls. All analyses were run separately by sex. This research was conducted under conditions of informed consent of all adolescents and their mothers, and with human subject clearance from the Institutional Review Boards of the Emory University Medical School and the University of Chapel Hill, NC.

Leptin measurement

Participants were asked to fast overnight for 12 h, and blood samples were collected in clinics the following morning using EDTA-coated tubes. Mean time of blood draw was 8:06 a.m. (range 7:18–9:09 a.m.). After separation, samples were frozen and shipped on dry ice to the University of North Carolina at Chapel Hill for analysis. Plasma samples were analyzed for leptin using a commercially available EIA kit (Linco Research, St. Louis, MO) on a Dynatech 5000 analyzer. Average within assay precision for repeat determinations of control samples across the assay range is reported by the manufacturer to be 2.6% coefficient of variation (CV; standard deviation/mean). Between-assay reliability is 3.8% CV. All samples remained frozen at −70°C until ready for analysis.

Sample selection

During the 1998–1999 survey, 2089 adolescents (68% of the original cohort of 3080 liveborn infants), ages 14–16 years, were located and interviewed. Of these, 1,969 had available measurements of birth outcomes, gesta-tional age, and current measurements. From these individuals, a sub-sample was selected for an additional study of cardiovascular disease risk. Individuals from the larger sample were sampled at random for the CVD study from within two birth weight strata. To ensure adequate numbers of lower birth weight individuals (for analyses not presented here), individuals with birth weights equal to 2,600 g or less were over-sampled compared to their frequency in the larger sample. Final samples for the CVD sub-study include 154 of the 316 (48.7%) males and females with a birth weight ≤ 2.6 kg and 449 of the 1,653 (27.2%) individuals of higher birth weight (total sub-sample = 603). Of the 603 individuals selected for blood sample collection, seven were excluded from the leptin analysis because of insufficient plasma for analysis (two individuals) or incomplete data on diet and anthropometrics in 1998 (five individuals), yielding a final sample of 596 individuals with complete data and leptin measurement. Sample design was corrected for in the analysis (see below).

Baseline characteristics of those adolescents who were included in the 1998 follow-up were compared with those who were in the sample at baseline (singleton, liveborn infants). Mean birth weight of those lost to follow-up was roughly 50 g less than those retained in the sample. This is most likely attributable to the higher mortality rates among low birth weight infants. Birth length did not differ significantly in the two groups. Those lost to follow-up were more likely to have been urban residents (82.5% urban *vs*. 73.5% in the retained sample), but there were no significant differences in household assets, maternal education or maternal height, age or parity. We also assessed potential biases in the sub-sample selected for leptin analysis. Consistent with sampling design, females included in the leptin study had significantly lower birth weight, current height, and current weight (all $P < 0.05$) compared to those excluded, while these differences did not reach significance in males. There were no differences in body mass index, skinfold thickness, income, or dietary fat intake among individuals who were and were not included in the leptin study.

Statistical analyses

All analyses were performed with version 8 of the Stata Statistical Package (College Station, TX). To get an unbiased estimate of distributional characteristics (e.g. mean leptin or dietary energy intake of children), the observations were weighted such that both birth weight strata would be represented in the estimate in proportion to their occurrence in the population. Probability sampling weights (pweights) for each strata were calculated as the inverse of the within-strata sampling fraction, and the svymean procedure of STATA was used to estimate distributional characteristics. Because leptin, adiposity and diet variables were all right-skewed, all were log-transformed prior to correlational or regression analysis. In addition, the shape of the relationship of leptin to skinfold thickness was examined using the Stata Lowess smoother. In this case, a locally weighted regression of leptin on triceps skinfold was examined to explore nonlinearities.

RESULTS

Table 1 describes the metabolic, anthropometric, and lifestyle characteristics of the sample. As expected, males

TABLE 1. *Characteristics of Filipino adolescents included in this study*

Variable	Mean (SD)[a]	
	Male ($n = 293$)	Female ($n = 303$)
Leptin (ng/ml)	0.78 (0.86)	3.57 (2.26)
Height (cm)	158.4 (6.8)	148.9 (5.2)
Weight (kg)	46.7 (8.6)	41.8 (7.0)
BMI (kg/m^2)	18.5 (1.7)	18.8 (1.7)
Overweight % (n)	2.3 (7)	2.1 (6)
Obesity % (n)	0	0.7 (2)
Waist/hip ratio	0.90 (0.06)	0.77 (0.04)
Triceps skinfold (mm)	8.2 (3.4)	14.6 (3.5)
Subscapular skinfold (mm)	7.7 (3.4)	11.5 (3.5)
Energy (kcal)	1936 (804)	1341 (557)
Fat intake (% kcal)	21.3 (12.0)	22.7 (12.2)
Age (years)	15.6 (0.5)	15.0 (0.3)
Household income (pesos)	3693 (2964)	3413 (3352)
Urban (%)	81.4	73.5
Maturity[b]	3.28 (0.9)	13.1 (1.0)

[a] All sex differences significant at $P < 0.00001$, except BMI, % kcal from fat, and 1983 and 1998 income (NS).
[b] 5-Level pubic hair stage in males, menarcheal age in females.

Fig. 1. Mean leptin plotted on mean body mass index in adolescent populations. From this study: males (x) and females (square). See Table 2 for references.

were taller and heavier, and had thinner skinfolds compared to females. The population was very lean, and both males and females had a low BMI relative to other adolescent populations. Based upon IOTF age- and sex-specific criteria (Cole et al., 2000), overweight and obesity were nearly absent in both sexes. Leptin was also low relative to values reported for other adolescent populations (Fig. 1 and Table 2).

Table 3 presents the results of two sets of regression models: the first column reports unadjusted models of the relationship between log-transformed leptin and each anthropometric measure considered alone. Because body composition measures tend to be highly intercorrelated, the second, adjusted column presents regression coefficients and partial R^2 for each anthropometric measure after inclusion of triceps skinfold (the strongest predictor of leptin in both sexes) in the model. As expected, leptin was strongly positively related to skinfold thicknesses in both sexes. Although males had lower leptin than females, more of the variation in leptin in males was explained by skinfold thickness, and there was also a sex difference in the relationship of skinfold thickness in each regional depot with circulating leptin. In males, triceps skinfold thickness alone explained 40.2% of the variance in leptin ($P < 0.0001$). While all other anthropometric variables other than waist-hip-ratio (WHR) were strong positive predictors of leptin among males, none of these relationships remained significant after adjusting for triceps skinfold. The pattern of relationships was different in the females. Similar to males, triceps skinfold was the strongest individual predictor of leptin. Unlike in males, subscapular skinfold, weight, and the BMI all remained significant positive predictors of leptin after adjusting for triceps.

The differences in adiposity and leptin by maturational status were evaluated using menarcheal age in females and self-assessed PH stage in males (Table 4). Although not directly comparable measures, mean levels of adiposity and leptin across these scales provide insights into the direction of change with maturation for these variables, and whether this differs by sex (Figs. 2, 3, and 4). As observed in other populations (Ankarberg-Lindgren et al., 2001; Apter, 2003; Brandao et al., 2003), both tri-
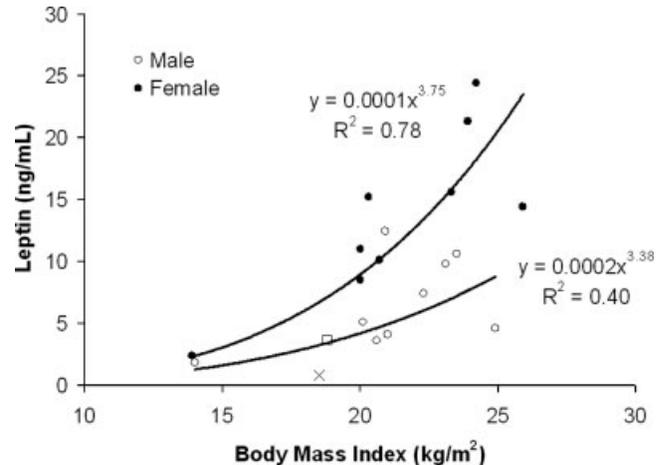
ceps and subscapular skinfolds were thicker in females who were more mature at the age of skinfold measurement (ANOVA F ratios 15.6 and 16.7 respectively, both $P < 0.0001$, df 4, 299). Leptin levels roughly paralleled the differences in adiposity among females varying in maturational status (see Fig. 4). Leptin was higher among girls who were more mature, with 60% higher leptin among the most mature girls compared to those least mature at the time of measurement (F ratio 10.5, $P < 0.0001$, df 4, 299). However, these maturity-based differences in leptin were no longer significant after holding triceps and subscapular skinfold thicknesses constant in a multivariate model (partial F test $P = 0.13$ for leptin by maturity stage). Among males, skinfolds increased incrementally across advancing PH stages (ANOVA both $P < 0.0001$), with 35 and 55% higher triceps and subscapular skinfolds, respectively, among individuals in PH5 compared to those in PH1 (ANOVA F ratios 5.0 and 9.8 respectively, both $P < 0.0001$, df 4, 289). Despite the thicker skinfolds among mature males, there were no differences in leptin levels by PH stage, with or without adjusting for triceps or subscapular skinfolds ($P > 0.3$ for both).

There were few significant relationships between leptin and lifestyle characteristics in either sex, as represented by dietary intake of energy and fat, activity level, and urban residence (Table 5). Leptin was significantly positively correlated to intake of energy and fat and to activity level in females. However, when leptin was adjusted for skinfold thickness, only percent dietary energy from fat remained significantly and positively related to leptin. Among males, activity level was a significant, positive predictor of leptin, but this relationship was not independent of triceps skinfolds. Urban residents had higher leptin in both sexes, although this relationship was only independent of skinfold thickness in males.

Following Collinson et al. (2005), Figure 5 presents "discrimination indices", or the ratio of mean leptin in the fourth vs. first quartile for a variety of different measures of body composition. These ratios reflect the ability of leptin to discriminate between extremes of each anthropometric variable, and by implication, the value of leptin as a circulating signal of the dimension of nutri-

TABLE 2. Leptin in adolescents[a]

Population	Males			Females			Reference
	Leptin	BMI	Age	Leptin	BMI	Age	
Cebu	0.77 (0.05)	18.5 (0.1)	15.5 (0.03)	3.6 (0.13)	18.8 (0.1)	14.8 (0.02)	This study
Korea	4.6 (3.0)	24.9 (3.3)	15.5 (1.7)	14.4 (6.6)	25.9 (3.9)	15.4 (1.5)	Park et al., 2004
Brazil	3.6 (4.3)	20.6 (3.5)	12.9 (2.0)	8.5 (7.7)	20.0 (4.1)	11.6 (1.5)	Brandao et al., 2003
Taiwan	4.1 (4.4)	21.0 (3.9)	13.3 (0.9)	10.1 (6.4)	20.7 (3.4)	13.3 (0.9)	Wu et al., 2002
Mexican–American	5.1 (3.6)	20.1 (3.7)	11.4 (4.2)	11.0 (8.2)	20.0 (4.0)	10.9 (4.5)	Butte et al., 2005
Pima	10.6	23.5 (5.9)	10	24.4	24.2 (5.5)	10	Salbe et al., 2002
African American	7.4 (13.4)	22.3 (4.0)	15.2 (2.2)	21.3 (14.7)	23.9 (4.9)	15.3 (2.2)	Degawa-Yamauchi et al., 2003
US	9.8 (9.7)	23.1 (5.3)	13.4 (1.0)	15.6 (10.2)	23.3 (5.0)	13.3 (0.8)	Hackney et al., 2003
Italy	12.45 (9.94)	20.9 (4.8)	8.6 (1.2)	15.19 (12.25)	20.3 (4.4)	8.31 (1.3)	Moore et al., 2004
Gambia	1.83 (0.47)	14.0 (1.0)	8.0 (0.7)	2.36 (0.91)	13.9 (1.0)	8.00 (0.68)	Moore et al., 2004

[a] Mean (SD).

TABLE 3. Regression models relating measures of body composition with leptin (log ng/ml), before and after adjusting for triceps skinfold thickness[a]

	Unadjusted β (SE)	P-value	R^2	Adjusted β (SE)	P-value	R^2
Males (n = 293)						
Triceps	1.32 (0.09)	0.000	0.402	–	–	–
Subscapular	1.21 (0.12)	0.000	0.266	0.01 (0.18)	0.967	0.000
BMI	0.12 (0.02)	0.000	0.191	0.01 (0.02)	0.487	0.001
Weight	0.04 (0.00)	0.000	0.176	0.00 (0.01)	0.984	0.000
Waist circ	0.06 (0.01)	0.000	0.206	0.01 (0.01)	0.307	0.002
WHR	−0.37 (0.73)	0.613	0.001	−0.51 (0.57)	0.370	0.002
Height	0.02 (0.01)	0.003	0.029	−0.01 (0.01)	0.213	0.003
Females (n = 303)						
Triceps	1.06 (0.09)	0.000	0.306	–	–	–
Subscapular	0.95 (0.08)	0.000	0.300	0.49 (0.16)	0.002	0.021
BMI	0.11 (0.01)	0.000	0.270	0.05 (0.01)	0.001	0.028
Weight	0.04 (0.00)	0.000	0.249	0.02 (0.01)	0.004	0.019
Waist circ	0.05 (0.01)	0.000	0.209	0.01 (0.01)	0.118	0.005
WHR	0.56 (0.75)	0.460	0.002	−0.57 (0.63)	0.369	0.002
Height	0.01 (0.00)	0.011	0.021	−0.00 (0.00)	0.923	0.000

[a] Coefficients for triceps and subscapular skinfolds are log-mm. R^2 in the adjusted models represent percent leptin variance explained beyond what is explained by triceps.

TABLE 4. Characteristics of adolescents by maturational stage variables

	Maturational status[a]				
	1	2	3	4	5
Males (n = 293)					
Age	15.4 (0.5)	15.3 (0.5)	15.5 (0.5)	15.6 (0.5)	15.8 (0.4)
Height	151.5 (7.6)	155.3 (7.0)	157.5 (5.9)	160.2 (6.2)	162.1 (4.0)
Weight	38.5 (4.8)	43.2 (8.2)	44.9 (6.8)	49.3 (8.9)	52.6 (7.3)
n	13	44	107	116	13
Females (n = 303)					
Age	14.9 (0.3)	14.9 (0.3)	14.8 (0.3)	14.7 (0.3)	14.8 (0.4)
Menarcheal age[b]	14.6 (0.5)	13.8 (0.4)	13.1 (0.4)	12.6 (0.5)	11.8 (0.6)
Height	145.5 (5.7)	147.7 (5.5)	148.7 (4.7)	150.1 (6.0)	150.1 (6.2)
Weight	36.5 (5.5)	40.6 (6.3)	42.0 (5.2)	43.2 (5.8)	44.1 (6.8)
n	52	71	56	63	61

[a] Mean (SD) stratified on self-assessed pubic hair stage in males and quintiles of maturity based upon menarcheal age in females.
[b] Twenty girls in stage 1 had not yet reached menarche (n = 283).

tional status represented by each measure. For females, the indices were similar across most anthropometric measures other than the WHR, with mean leptin levels in the highest quartile roughly twice the mean among individuals in the lowest quartile for that measure. In contrast, there were marked differences in the ability of leptin to discriminate between the extremes of different anthropometric measures among males, with the highest

discrimination index for triceps (3.2) and lowest for the WHR (1.1).

To further explore the relationship between triceps skinfold and leptin, Figure 6 plots leptin values *vs.* triceps skinfold thickness and fitted with a Lowess smoother. This locally-weighted regression method reduces the influence of outliers, and the estimated regression line faithfully follows the data. In males, the relationship of
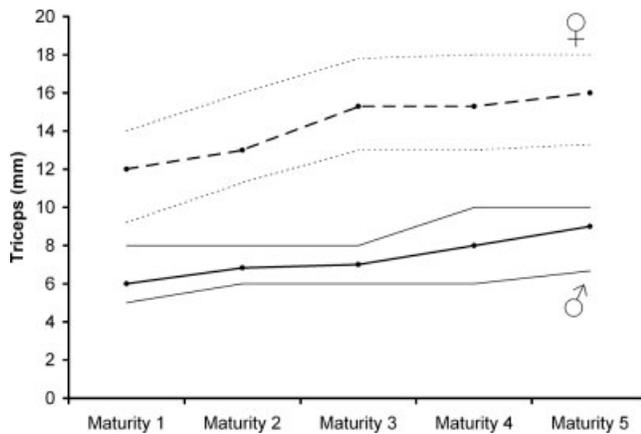
Fig. 2. Differences in triceps skinfold thickness by maturational status in females and males. Maturity scales are based upon quintiles of menarcheal age in females and self-assessed PH stage in males. Values are stage-specific medians (dark lines) and 25th and 75th centiles (thin lines) of the distribution in each sex.
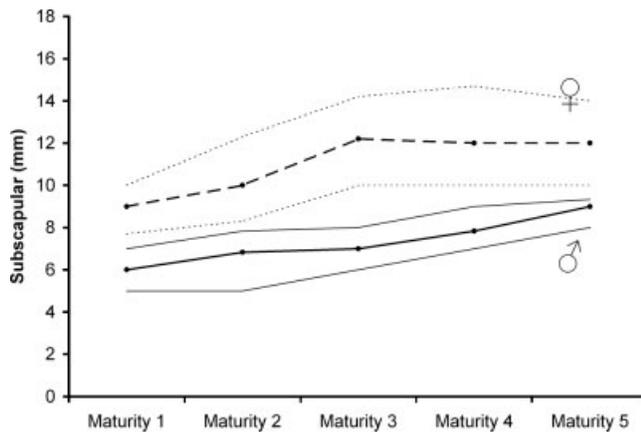

Fig. 4. Differences in leptin by maturational status in females and males. Maturity scales are based upon quintiles of menarcheal age in females and self-assessed PH stage in males (see Fig. 2 for explanation).

Fig. 3. Differences in subscapular skinfold thickness by maturational status in females and males. Maturity scales are based upon quintiles of menarcheal age in females and self-assessed PH stages in males (see Fig. 2 for explanation).

triceps skinfold thickness to leptin was nonlinear, with little change in leptin across much of the lower region of the triceps distribution. Leptin values began to increase in a curvilinear pattern above roughly 1 ng/ml. In females the relationship was linear, with monotonic increases in leptin associated with increasing triceps skinfold thickness.

DISCUSSION

The Filipinos in this study were lean and had lower circulating leptin concentrations than reported previously for adolescents (see Fig. 1). In a recent study of adolescents in Korea, mean male and female leptin levels were six and four times higher, respectively, than their Cebu counterparts (Park et al., 2004). Although the Cebu findings were similar to the few subsistence-level populations for which data are available (Zimmet et al., 1998; Bribiescas, 2001, 2005; Iputo et al., 2001; Moore et al., 2004), the leptin values documented here stand out as
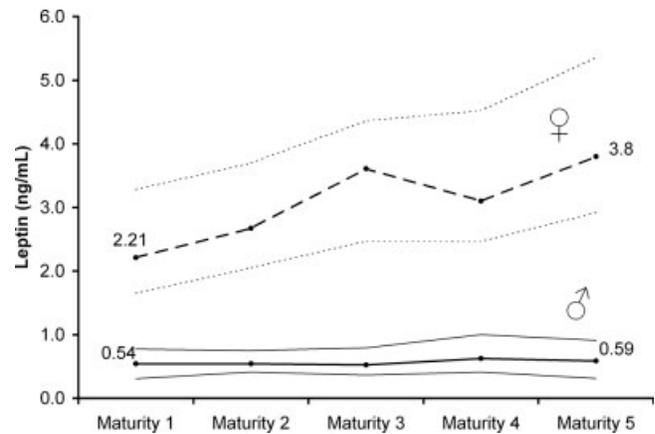
among the lowest ever recorded in a healthy sample, and help illustrate the great range of leptin variability across human populations.

As expected, there were large sex differences in body composition and leptin concentration in the sample. Although the maturational status indices used in males and females are not directly comparable, they provide a rough sense for the direction of change in adiposity and leptin as males and females mature. There was an increase in leptin across all 5 levels of maturity among females, despite the fact that mean skinfold thickness did not vary significantly across the three most mature groups. The pattern was different among males: adiposity increased consistently across each maturational stage, while mean leptin did not. This failure to find increased leptin among more mature males, despite their thicker skinfolds, may indicate an influence of testosterone, which has been shown to reduce leptin production (Luukkaa et al., 1998; Dicker et al., 2004). Conversely, the increase in leptin among the more mature females despite their lack of thicker skinfolds could reflect the effects of estrogens in enhancing leptin production (Shimizu et al., 1997). It may also be that pubertal deposition of fat among females, which prominently includes the thigh and calf, was not fully captured by the two measures of skinfold thickness available to this study.

By reflecting changes in energy stores, circulating leptin is believed to function as a feedback signal that helps the brain modify intake and expenditure to maintain a stable body weight (Campfield et al., 1995; Bjorbaek and Kahn, 2004). The strong correlations between leptin and skinfold thickness at Cebu are consistent with this role of leptin as a signal of energy reserves (Spiegelman and Flier, 1996). It is notable, however, that relationships between leptin and energy status varied markedly by sex and by regional fat depot. In males, no body composition measure related to leptin independent of triceps skinfold thickness. The thickness of subcutaneous fat in the subscapular region explained no additional variance in leptin in a model that included triceps, and the P-value for subscapular skinfolds in this joint model was close to 1.0. Although triceps were also the strongest predictor of leptin in females, subscapular

TABLE 5. Pearson correlation coefficients relating log-leptin to lifestyle measures[a]

	Males ($n = 293$)		Females ($n = 303$)	
	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[c]
Energy (kcal)	0.09	0.04	0.18**	0.03
Fat (g)	0.08	0.02	0.18**	0.03
Physical activity (kcal/day)	0.16**	−0.08	0.12*	−0.01
Urban residence[d]	1.21*	1.23**	1.19**	1.07

[a] *$P < 0.05$, ** $P < 0.01$.
[b] Adjusted for triceps skinfold thickness.
[c] Adjusted for triceps and subscapular skinfold thicknesses.
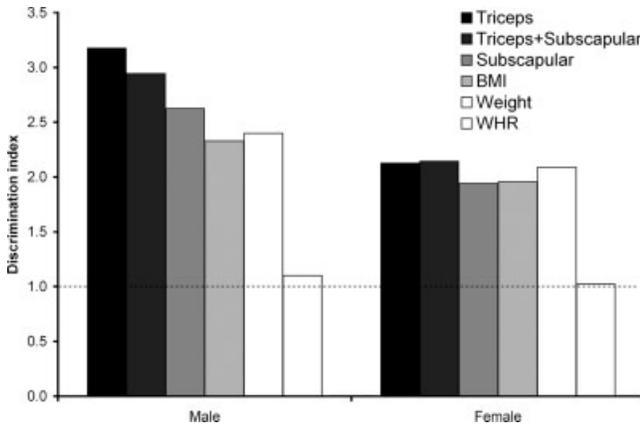[d] Leptin in urban minus leptin in rural (ng/ml) before and after adjusting for skinfold thickness.

Fig. 5. Leptin discrimination indices for different anthropometric indicators of body composition in males and females. Following Collinson et al. (2005), indices were calculated as the ratio of mean leptin in the fourth quartile to the mean of leptin in the first quartile for that anthropometric measure.

Fig. 6. Lowess regression of leptin on triceps skinfold thickness in females and males.

skinfold, the BMI and body weight all predicted leptin independent of triceps, suggesting that a wider array of regional depots contribute to the higher circulating leptin concentrations in females. These sex differences were also reflected in the discrimination ratios, which showed that leptin levels best signaled differences in triceps skinfolds in males, but were about equally effective at discriminating weight, BMI, and several measures of adiposity in females.

The WHR was unrelated to leptin in both sexes, providing additional evidence that leptin production differs by adipose depot. Although the utility of the WHR as a measure of abdominal adiposity has been questioned (Daniel et al., 2003), low or no production of leptin by visceral adipocytes has been documented in humans (Van Harmelen et al., 1998; Russell et al., 2001). Visceral fat contributes less to circulating leptin concentrations when compared to subcutaneous fat depots, with peripheral subcutaneous depots typically most strongly related to leptin (Eriksson et al., 1999; Hu et al., 2001; Douchi et al., 2002; Park et al., 2004). Although the functional significance of these differences in leptin production remain poorly understood, it may be important that changes in the more labile central depots, which are involved in maintaining short-term energy balance in response to acute changes in energy intake and expenditure, be "invisible" to leptin-sensing centers of the central nervous system that are charged with regulating long-term energy balance.
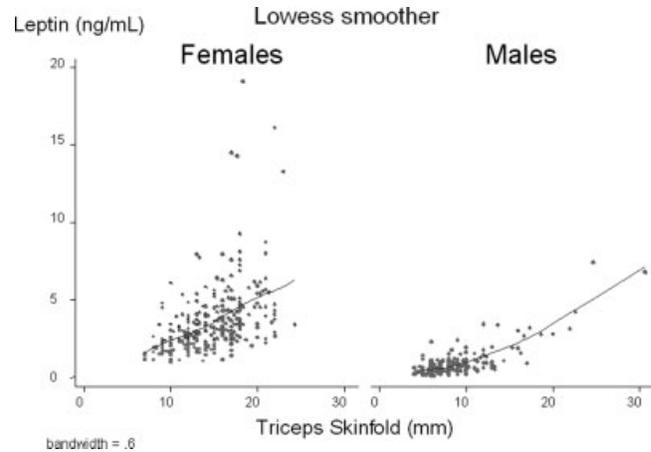
Leptin sensitivity in evolutionary perspective

Despite their very low levels of body fat and low leptin concentrations, the correlation between leptin and adiposity was stronger among males. It is notable, however, that this was almost entirely accounted for by relatively high leptin among males with the highest levels of body fat. If the 10% of males with thickest triceps skinfolds were excluded from the analysis, the percentage of the variation in leptin accounted for by triceps skinfolds was reduced to 14.9% (down from 40.2%), and indeed, triceps skinfold thickness explained a mere 3% of leptin variation among the leaner half of the male sample. A similar finding of a weak or nonsignificant correlation between leptin and adiposity has been noted in other samples of lean males (Bribiescas, 2001).

The shape of the relationship between skinfolds and leptin, and a relatively narrow range of leptin variability, hints at a high sensitivity to small changes in leptin in these lean males. Moving across the leanest half of the male sample, from the 10th to the 50th percentile of triceps skinfolds, predicts an increase in leptin from 0.36 to 0.57 ng/ml. If leptin functions as a signal of energy status in these males, the minimal variation in the hormone suggests that the brain is capable of responding to subtle changes in its circulating concentration as they gain and lose weight. In addition, while changes in leptin were modest across much of the male triceps distribution, there was a qualitative increase in leptin at the highest levels of adiposity, as indicated by the upturn of the Lowess function (see Fig. 6). A nonlinear increase in leptin with increasing body fat has been documented in

other populations with higher mean adiposity (Luke et al., 1998), and could reflect an increase in the production of leptin relative to fat mass (Considine et al., 1996). The ability of the brain to sense changes in leptin may be impaired at higher levels of body fat as leptin receptors at the blood brain barrier become saturated (Banks et al., 2000; Banks, 2003). Our finding of a low mean and narrow range of leptin variability, coupled with clinical evidence for leptin dysregulation among individuals with more body fat, suggests that the hormone likely evolved to monitor much lower levels of adiposity than is typical in many western, industrialized populations today (Bribiescas, 2001).

CONCLUSIONS

These findings add to the small but growing list of studies documenting very low leptin in chronically lean or marginally nourished populations, compared to the over-nourished populations that are more typically the subject of leptin research. The present findings support the interpretation that the leptin-body fat regulatory system was "designed" to operate at much lower levels of energy status than observed in many studies in western societies, where a chronic state of positive energy balance and weight gain are common and may lead to a progressive increase in body fat and central leptin resistance. Additional research among lean populations will prove critical to understanding the leptin-body weight system and its role in regulating energy balance.

ACKNOWLEDGMENTS

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